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<b>(21) International Application Number:</b> PCT/US97/19831 <b>(22) International Filing Date:</b> 31 October 1997 (31.10.97)  <b>(30) Priority Data:</b> 60/030,282      4 November 1996 (04.11.96)      US  <b>(71) Applicant (for all designated States except US):</b> UNION CARBIDE CHEMICALS & PLASTICS TECHNOLOGY CORPORATION [US/US]; 39-Old Ridgebury Road, Danbury, CT 06817-0001 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DONABEDIAN, David, H. [-/US]; Apartment 46H, 70 JFK Boulevard, Somerset, NJ 08873 (US). MARLIN, Lawrence [-/US]; 7 Wright Street, Bridgewater, NJ 08807 (US). CLARK, Elke, M., A. [-/US]; 12 Country Club Drive, Ringoes, NJ 08551 (US).  <b>(74) Agent:</b> WIGGINS, Karen, Johnson; Union Carbide Chemicals & Plastics Technology Corporation, 39-Old Ridgebury Road, Danbury, CT 06817-0001 (US).		<b>(81) Designated States:</b> BR, CA, CN, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>Without international search report and to be republished upon receipt of that report.</i>
<b>(54) Title:</b> METHOD FOR ENHANCING THE SOLUBILITY OF SUBSTANTIALLY WATER-INSOLUBLE COMPOUNDS  <b>(57) Abstract</b>  Methods for enhancing the water-solubility of substantially water-insoluble compounds are disclosed by combining such compounds with a water-soluble polymer, e.g., polyalkylene oxide polymer or a cellulose ether, having a molecular weight of from about 50,000 to 7,000,000 grams/per gram in an amount effective to enhance the water-solubility of the compound in an acidic environment, e.g., pH less than about 5. Compositions comprising the compounds having enhanced water solubility are also disclosed.		

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## METHOD FOR ENHANCING THE SOLUBILITY OF SUBSTANTIALLY WATER-INSOLUBLE COMPOUNDS

### Field of the Invention

The present invention generally relates to methods for enhancing the water-solubility of substantially water-insoluble compounds by combining such compounds with certain water-soluble polymers.

### Background of the Invention

Many hydrophobic drugs have limited solubility and dissolution rates due to their low water solubility. The bioavailabilities of many poorly water-soluble drugs are limited by their dissolution rates, which are in turn controlled by the surface area that they present for dissolution. Consequently, particle size reduction has been used to improve the availability of drugs, e.g. griseofulvin (Atkinson et al., *Antibiot. Chemotherapy* 12, 232, 1962), and sulphisoxazole (Fincher et al. *J. Pharm. Sci.*, 4, 704, 1965). However, unless the formulation of micronized drugs (Yamamoto et al. *J. Pharm. Sci.*, 65, 1484, 1976) is carefully controlled, the increase in availability may not be achieved since aggregation (Lin et al., *J. Pharm. Sci.*, 57, 2143, 1968) and agglomeration (Finholt et al., *Med. Norsk. Farm. Selskap.*, 28, 17, 1966), or air adsorption may result in poor powder wettability reducing the effective surface area.

With this in mind, techniques involving solvent deposition, lyophilization, solvate formation, micelle formation with the use of surfactants, and solid dispersion have been developed to increase the availability of drugs (Jun et al., *J. Kor. Pharm. Sci.* 20, 1120, 1990).

-2-

The concept of solid dispersions was disclosed by Sekiguchi and Obi (*Chem. Pharm. Bull.* 9, 866, 1961). In their study, the eutectic of the poorly water-soluble drug, sulphathiazole, and the physiologically inert, water-soluble carrier, urea, possessed higher absorption and excretion after oral administration than sulphathiazole alone. Other water-soluble carriers commonly used in solid dispersions include polyethylene glycol ("PEG") (Simonelli et al *J. Pharm. Sci.* 65, 3, 355, 1976 and Chin, *Arch. Pharm. Res.* 2 (1), 49, 1979) and polyvinyl pyrrolidone (*Kollidon® Polyvinylpyrrolidone for the Pharmaceutical Industry*, Volker Buhler, BASF, Ludwigshafen, 88, 1993), and cyclodextrin (El Banna et al. *Pharmazie* 30, 788, 1985). These materials often have relatively low molecular weights, e.g., less than about 80,000 grams per gram mole and can have insufficient effectiveness in acidic environments, e.g., pH of less than about 5.

Accordingly, methods are desired to enhance the water-solubility of substantially water-insoluble compounds particularly in acidic environments. Improved compositions having such enhanced solubility are desired which can be delivered from both solid and liquid forms.

#### Summary of the Invention

In accordance with the present invention, improved methods for enhancing the water solubility of substantially water-insoluble compounds are provided. The methods involve combining the substantially water-insoluble compounds with an effective amount of a water-soluble polymer having a weight average molecular weight from about 50,000 to about 7,000,000 grams/gram mole in an amount

effective to enhance the water solubility of compound in an acidic environment, e.g., less than a pH of about 5.

By virtue of the present invention, it is now possible to enhance the water solubility of such substantially water-insoluble compounds by at least about 10 percent and up to about 500 percent or more. As a result, when the methods of the present invention are used to enhance the water solubility of substantially water-insoluble drugs, such as, for example, ibuprofen or tolbutamide, the amount of ibuprofen or tolbutamide necessary to treat a patient can be reduced while still providing an effective amount of the drug to treat the condition. In addition, by selecting the appropriate molecular weight ranges of the water-soluble polymers or mixture polymers, the release profile of the compound in solution can be adjusted to the desired rate.

Compositions comprising the substantially water-insoluble compounds in combination with the water-soluble polymers are also provided by the present invention.

#### Detailed Description of the Invention

The particular substantially water-insoluble compounds suitable for use in accordance with the present invention are not critical. Typically, such compounds will have a water solubility of less than 1,000 parts per million by weight ("ppmw") and preferably less than about 600 ppmw. As used herein, the term "water solubility" means the amount of the compound or polymer which is soluble in distilled water (pH= 7.0) at 25° C and one atmosphere, unless stated otherwise. Typical water-insoluble compounds include for example, drugs, i.e., compounds which have a medicinal, pharmaceutical, therapeutic or diagnostic effect on mammals as well as other compounds, such as, for

example, antimicrobials, biocides, inks, colorants, preservatives, additives and the like.

Specific classes of drugs which may be utilized in the methods and compositions of the present invention, include for example, abortifacients, hypnotics, sedatives, tranquilizers, anti-inflammatory agents, antihistamines, anti-tussives, anti-convulsants, muscle relaxants, anti-tumor agents; for example those of the treatment of malignant neoplasia, local anaesthetics, anti-parkinson agents, topical or dermatological agents, diuretics, for example those containing potassium, such as potassium iodide preparations, for example those of the treatment of mental illness, for example preparations containing lithium for use in the treatment of manic depression, anti-spasmodics, anti-ulcer agents, preparation containing various substances for the treatment of infection by pathogens including anti-fungal agents, for example metronidazole, anti-parasitic agents and other antimicrobials, antibiotic agents, antibacterial agents, antiseptic agents, anti-malarials, cardiovascular agents preparations containing hormones, for example androgenic estroneic and progestational hormones, notably steroids such as oestradiol, sympathiomimetic agents, hypoglycaemic agents, nutritional agents, preparations containing enzymes of various types of activity, for example chymotrypsin, preparations containing analgesics, for example aspirin, and agents with many other type of action including nematocides and other agents of veterinary application, contraceptives, e.g., spermicides, virucides, vitamins, vasodilators, antacids, kerolytic agents, anti-diarrhea agents, anti-alopecia agents, glaucoma agents, dry-eye compositions, wound healing agents, and the like.

Examples of drugs that are substantially water-insoluble and suitable for use in accordance with the present invention include ibuprofen, ketoprofen, chlorthalidone, sulphadimadine, papaverine, sulphamethoxydiazine, hydrochlorothiazide, bendrofluazide, acetohexamide, diazepam, glipizide, nifedipine, griseofulvin, paracetamol, indomethacin, chlorpropamide, phenoxybenzamine, sulfathiazole, nitrazepam, furosemide, phenytoin, hydroflumethazide, tolbutamide, thialkylperazine maleate, dizoxin, reserpine, acetazolamide, methazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, acetaminophen, salicylic acid, methotrexate, acetyl sulfisoxazole, erythromycin, progestins, estrogenie, progestational, corticosteroids, and the like.

Preferred drugs suitable for use in accordance with the present invention are selected from the group consisting of ibuprofen, tolbutamide, sulfathiazole, and hydroflumethazide, and mixtures thereof.

The water-soluble polymers suitable for use in accordance with the present invention have a water-solubility (as defined above) of at least about 1.0 weight, and preferably at least about 2.0 weight percent.

Typically, the water-soluble polymers have a molecular weight of from about 50,000 to 7,000,000, preferably from about 80,000 to 4,000,000, more preferably from about 100,000 to 750,000 grams/gram mole. As used herein the term "molecular weight" refers to weight average molecular weight. Methods for determining the weight average molecular weight are known to those skilled in the art, and include for example, the method known as low angle light scattering.

The average particle size of the water-soluble polymers is not critical to the present invention, but is typically from about 0.01 microns to 1000 microns and preferably from about 50 microns to 150 microns.

Preferably, the water-soluble polymers have alkylene oxide functionality. More preferably, the alkylene oxide is selected from the group consisting of ethylene oxide, propylene oxide and mixtures thereof. Especially preferred polymers include polyalkylene oxides and alkoxylated polysaccharides.

Polyalkylene oxide polymers typically having from about 2 to about 4 carbon atoms per monomeric molecule polymers may be used in accordance with the present invention. Ethylene oxide and propylene oxide monomers are preferred. Polyethylene oxide polymers are especially preferred for use in accordance with the present invention. The polyethylene oxide polymers include, for example, homopolymers of ethylene oxide and copolymers of ethylene oxide with one or more polymerizable olefin oxide comonomers. The particular comonomer, when used in accordance with the present invention, is not critical and may contain hydrocarbon substituents such as alkyl, cycloalkyl, aromatic, alkene and branched alkyl groups. However, the amount of comonomer, e.g., 1,2-propylene oxide, must not exceed that which would cause the polyethylene oxide to become insoluble in water. Typical olefin oxide comonomers include 1,2-propylene oxide, 2,3-butylene oxide, 1,2-butylene oxide, styrene oxide, 2,3-epoxy hexane, 1,2-epoxy octane, butadiene monomide, cyclohexene monoxide, epichlorohydrin, and the like.

Polyalkylene oxides, such as for example polyethylene oxide, suitable for use in accordance with the present invention are available



from Union Carbide Corporation, Danbury, CT. Further details concerning the polyalkylene oxide polymers suitable for use in accordance with the present invention are known to those skilled in the art.

Alkoxyated polysaccharides, also referred to as polysaccharide ethers, are suitable for use in accordance with the present invention.

The polysaccharide starting materials suitable for use in accordance with the present invention include naturally occurring, biosynthesized and derivatized carbohydrate polymers or mixtures thereof. Such materials encompass high molecular weight polymers composed of monosaccharide units joined by glycosidic bonds. These materials may include, for example, the entire starch and cellulose families; pectin, chitosan; chitin; the seaweed products such as agar and carrageenan; alginate; the natural gums such as guar, arabic and tragacanth; bio-derived gums such as xanthan; and the like. Preferred starting materials include cellulose derivatives conventionally employed for the preparation of cellulose ethers, such as, for example, chemical cotton, cotton linters, wood pulp, alkali cellulose and the like. Such materials are commercially available.

The molecular weight of the polysaccharides suitable for use in accordance with the present invention typically ranges from about 50,000 to 2,000,000 grams per gram mole and preferably ranges from about 80,000 to 250,000 grams per gram mole.

The particular derivatizing agent, e.g., alkyl halides or alkylene oxides, used to derivatize the polysaccharides is not critical to the present invention. Suitable alkylene oxides for use in accordance with the present invention comprise from about 2 to 24, preferably from about 2 to 5 carbon atoms per molecule. Examples include ethylene

oxide, propylene oxide and butylene oxide. Typically, the ether substituent is derivatized onto the cellulose by reacting the polysaccharide with an alkylene oxide, preferably ethylene oxide. The amount of ether substitution is typically from about 1.5 to 6 and preferably from about 2 to 4 moles of ether substituent per mole of polysaccharide ether. Suitable alkyl halides include, for example, ethyl chloride or methyl chloride.

The polysaccharide ethers may be substituted with one or more desired substituents, e.g., cationic, anionic and/or hydrophobic substituents. Hydrophobic substituents are known in the art and typically comprise alkyl, alkene, aryl-alkene or aryl-alkyl groups having about 8 to 24 carbon atoms per molecule. Hydrophobically-modified cellulose ethers are described, for example, in U.S. Patent Nos. 4,228,277, 5,120,328 and 5,504,123 and European Patent Publication 0 384 167 B1. Cationic, hydrophobically modified cellulose ethers are described, for example, in U.S. Patent No. 4,663,159. The substitution level of each such substituent on the polysaccharide ether is typically from about 0.001 to 0.1 and preferably from about 0.004 to about 0.05 moles of substituent per mole of polysaccharide ether. More than one particular substituent can be substituted onto the polysaccharide ether.

The viscosity of the polysaccharide ethers typically ranges from about 1 to 8000 centipoise, preferably from about 100 to 3000 centipoise. Unless otherwise indicated, as used herein the term "viscosity" refers to the viscosity of a 1.0 weight percent aqueous solution of the polymer measured at 25°C with a Brookfield viscometer. Such viscosity measuring techniques are known in the art and are described in ASTM D 2364-89. The average particle size of the

polysaccharide ethers is not critical, but is preferably from about 0.01 to 1000 microns and more preferably from about 50 to 400 microns.

Preferred polysaccharide ethers produced in accordance with the present invention, are cellulose ethers, including for example, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl methyl cellulose, carboxymethyl cellulose, hydroxyethyl carboxymethyl cellulose, and derivatives thereof.

The amount of the water-soluble polymer effective to enhance the water solubility of the substantially water insoluble compound typically ranges from about 1 to 500, preferably from about 20 to 300 and more preferably from about 50 to 250 grams of polymer per gram of compound. Such concentrations typically correspond to polymer concentrations of from about 0.1 weight percent up to about the solubility limit of the polymer in the aqueous liquid, e.g., 25 weight percent or less. More typically, the concentration of polymer ranges from about 0.1 to 5 weight percent, preferably from about 0.1 to 2 weight percent based on the total weight of the aqueous liquid.

The water-soluble polymer can be combined with the compound by physical mixing in a dry state, wet state or by melting the polymer, when a thermoplastic polymer is used either before or during the combination with the compound and melt blending the polymer with the compound. Further details concerning such blending techniques and apparatus suitable therefor are known to those skilled in the art.

Thus enhanced solubility can be achieved by either adding the substantially water-insoluble compound directly to an aqueous composition containing the water soluble carrier or by co-mixing in the melt state the carrier and substantially water-insoluble compound.

Unlike other techniques described in the literature, U. S. Pat. No's 4,687,662 (issued August 18, 1987), 4,689,218 (issued August 25, 1987), 4,834,966 (issued May 30, 1989), 4,861,797 (issued August 29, 1989), and WO 96/19973 (date of publication July 4, 1996) which incorporate the use of an effervescent agent to afford solubility to actives like ibuprofen, or surfactants, E. P. App. 0 228 164 A2 (date of publication August 7, 1987), no such agents are needed in the present invention. Nor is the use of an organic solvent needed to enhance the solubility of the substantially water-insoluble compound as described in U. S. Pat. No. 5,225,204 (issued July 6, 1993).

In addition to the water-soluble polymers used to enhance solubility, other polymers known to those skilled in the art may be used in accordance with the present invention. Such polymers, include for example, those selected from the group consisting of hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, cationic cellulose ethers, polyvinyl pyrrolidone, carboxyvinyl polymer, hydroxypropylmethyl cellulose phthalate, acetate phthalate, methyl meta-acrylate meta-acrylic acid copolymer, polyvinylacetal dialkylaminoacetate, dimethylaminoalkyl meta-acrylate meta-acrylic acid copolymer, 2-methyl-5-vinylpyridinemethyl acrylate meta-acrylic acid copolymer, citric acid, urea, succinic acid and amino acid. The concentration of polymers other than the water-soluble polymers suitable for use in accordance with the present invention is not critical and typically ranges from about 0.1 to 99 weight percent based on the total weight of water-soluble polymers, the compound and the other polymers. Further details concerning the selection and use of such other polymers are known to those skilled in the art.

-11-

Typically in accordance with the present invention, the amount of water-soluble polymer which is combined with the substantially water-insoluble compound in solution is effective to provide a solubility enhancement of at least 10 percent, preferably at least 20 percent, more preferably at least 30 percent, even more preferably at least about 50 percent, still more preferably at least about 100 percent, even further more preferably at least about 200 percent. More than one water-soluble polymer may be employed. Such solubility enhancements generally correspond to concentrations of soluble compound of at least 100 ppmw, preferably at least 150 ppmw and more preferably at least about 300 ppmw when prepared in aqueous liquid form.

The methods of the present invention can be utilized to provide stable compositions having enhanced solubility in any desired form. More specifically, the compositions of the present invention can be provided as either liquids, solids or combinations thereof. Typical forms can be films, tapes, laminates, gels, tablets, particles, aqueous solutions, dispersions and other pourable liquids. The physical characteristics of the compositions of the present invention will depend on the relative amounts of the polymers and compounds used in the compositions. For example, the concentration of polyalkylene oxide or the water-soluble polymer in a solid composition can range broadly from a very low concentration, e.g., 0.1 weight percent, to a very high concentration of 99 weight percent or more. Liquid compositions, especially for alkoxylated polysaccharide polymers will often comprise substantially smaller amounts of polymer often in the range 0.1 to about 5 weight percent.

Quite surprisingly, in addition to providing enhanced solubility the compositions of the present invention can also provide a sustained release of the compounds in the aqueous liquid. It has been found that when utilizing the water-soluble polymers having certain molecular weight ranges, the characteristics of the release profile can be adjusted as desired. More specifically, when it is desired to have a fairly continuous compound release profile, e.g., greater than 12 hours, then the water-soluble polymers in the molecular weight range of about 900,000 to 7,000,000 for the polyalkylene oxide polymers and 500,000 to 1,000,000 for the alkoxylated polysaccharide polymers are preferred. In contrast, when it is desired to provide an initially fast release profile followed by a slower release profile, polymers having a molecular weight in the range of from about 100,000 to 600,000 for the polyalkylene oxide polymers are preferred and 100,000 to 400,000 for the alkoxylated polysaccharide polymers are preferred.

The methods and compositions of the present invention have a wide variety of end use applications, such as for example, industrial applications and personal care applications. Typical industrial applications include, for example, the solubility enhancement of antimicrobial compounds, biocides, inks and colorants, preservatives, additives and the like. Typical personal care applications include, for example, various pharmaceutical and cosmetic compositions.

Typical drug tablets which may be utilized in accordance with the present invention can be made by any technique known to those skilled in the art such as for example, by direct compression, granulation with a suitable solvent followed by compression, melt fabrication and or by fabrication in dosage forms. Such drugs which are deliverable in solid form typically contain the compound, the

-13-

water-soluble polymer and other known ingredients, including for example, lactose, magnesium or calcium stearate, dicalcium phosphate, mannitol, and microcrystalline cellulose. The alkoxyated polysaccharide polymer compositions may also be delivered as a semi-solid/liquid dosage application such as often used for cold and headache medications. The equipment conditions and techniques for forming such compositions are known to those skilled in the art. Note, for example, U.S. Patent No. 5,273,758, issued December 28, 1993, U.S. Patent No. 4,343,789 issued August 10, 1982, and U.S. Patent No. 5,116,145, issued November 24, 1992.

Quite surprisingly, the water-soluble polymers of the present invention are effective to enhance the solubility of the compounds in an acid environment, preferably at a pH of less than about 5, more preferably less than about 3 and most preferably at gastric fluid acidity, e.g., about pH = 1.1.

The following Examples are presented for illustrative purposes and are not intended to limit the scope of the claims which follow.

#### EXAMPLE 1

Aqueous solutions of CELLOSIZE® HEC WP 09L (80,000 g/mol, Union Carbide Corp. Danbury, CT) were prepared in 100 milliliter ("mL") volumetric flasks and placed on magnetic stir plates at 25°C. The HEC based solutions ranged from 0.5, 1.0, and 2.0 percent by weight. To these solutions, an excess of drug was added to form saturated solutions which were allowed to stir for an additional 2 hours at 23°C. At the end of this period, small aliquots were removed and filtered through 0.45 micron ("m") filters and the filtrates were suitably diluted and blanked for absorbance measurements at the

-14-

appropriate wavelength using a UV-VIS spectrophotometer (Hewlett Packard). Drug solubility was determined from established calibration curves. Table 1 lists the data.

Table 1.

Solubility enhancement of ibuprofen in aqueous CELLOSIZ HEC polymer solutions.

Sample	Concentration (%w/v)	Ibuprofen Solubility (ppm)
CELLOSIZ WP-09L	0.0	50
CELLOSIZ WP-09L	1.0	140
CELLOSIZ WP-09L	2.0	230

CELLOSIZ HEC WP-09L showed an increase in ibuprofen solubility, on the order of fourfold, for a 2.0% (w/v) solution.

#### EXAMPLE 2

To determine if other commonly used binders in the pharmaceutical industry enhance ibuprofen solubility in water, the following material was also examined: METHOCEL® K100 LV Prem CR [hydroxypropylmethyl cellulose (HPMC) Dow Chemical Co., MW 23,000 g/mol] The HPMC polymer was dissolved in water following a procedure recommended by the vendor (Product Bulletin, Dow Chemical, Midland, MI.). In this procedure, the polymer was dispersed in cold water under high shear, and then the temperature was slowly raised to help solubilize the polymer. After solubilization, the temperature was allowed to cool to room temperature. The polymer was not readily dissolvable at room temperature. To these solutions, an excess of ibuprofen was added and analyzed as outlined in Example 1. The following data was obtained for these samples:



Table 2.

Comparison of solubility enhancement of ibuprofen in aqueous hydroxypropyl methylcellulose and hydroxyethyl cellulose solutions.

Sample	Concentration (%w/v)	Ibuprofen Solubility (ppm)
CELLOSIZ WP-09L	0.0	50
CELLOSIZ WP-09L	1.0	140
CELLOSIZ WP-09L	2.0	230
METHOCEL K100 <sup>a</sup>	1.0	50<
METHOCEL K100 <sup>a</sup>	2.0	50<

From this data, HPMC had very little if any effect on increasing the water solubility of ibuprofen relative to CELLOSIZ HEC WP-09L.

### EXAMPLE 3

To determine if hydroxyethyl cellulose could enhance the solubility of other classes of drugs, amine based drugs like tolbutamide (Sigma Chemical Co., St. Louis, MO) were investigated. Samples were prepared in the same manner as described in Example 1 with the following results in Table 3:

Table 3.

Solubility of tolbutamide in CELLOSIZ HEC WP 09 solutions.

Sample	Concentration (%w/v)	Tolbutamide Solubility (ppm)
CELLOSIZ HEC	0.0	75
CELLOSIZ HEC	0.5	200
CELLOSIZ HEC	1.0	175
CELLOSIZ HEC	2.0	300

-16-

It can be seen that the aqueous CELLOSIZ HEC based solutions were aiding in the solubilization of this amine based drug. At concentrations ranging from 0.5% to 2.0%, the solubility of tolbutamide increased from 75 ppm to 300 ppm. Without being bound to any particular theory, it appears that the solubilization of the drug may be taking place due to main chain interaction between the drug and polymer

The solubility increase of all these drugs was determined in water. Next, a medium with a lower pH, indicative of the pH of the stomach was investigated.

#### EXAMPLE 4

Samples were prepared in the same manner as described in Example 1. Physical dispersions of tolbutamide were prepared in CELLOSIZ HEC WP 09L in simulated gastric fluid (SGF, pH=1.1) at concentrations ranging from 0.5%-2.0%. Table 4 summarizes the pH both before and after drug addition as well as the maximum solubility of the drug in this medium. From this table, the solubility of tolbutamide did increase substantially from 75 ppm to 170 ppm in a 0.5% solution of hydroxyethyl cellulose. Hydroxyethyl cellulose not only increase the solubility of poorly water soluble drugs at neutral pH's but also increases solubility at low pH's.

Table 4

pH before and after drug addition in CELLOSIZ HEC WP 09L  
prepared in SGF.

Polymer	Conc. (w/v)	drug	pH before	pH after	Sol. (ppm)
HEC WP 09	0.0	tolbutamide	1.21	1.21	70
HEC WP 09	0.5	tolbutamide	1.21	1.21	170
HEC WP 09	2.0	tolbutamide	1.21	1.21	120

From this data, it appears that CELLOSIZ HEC seems to enhance the solubility characteristics of poorly water soluble drugs like ibuprofen and tolbutamide in aqueous mediums with ranging pH profiles.

#### EXAMPLE 5

Polyethylene oxide, another hydrophilic binder commonly used in the pharmaceutical industry, was investigated to determine if it could enhance the solubility of substantially water-insoluble compounds. This material, unlike hydroxyethyl cellulose is thermoplastic, that is, it can be re-melted and re-shaped without loss in molecular weight using conventional melt processing equipment.

In the following example, a process and technique are described to prepare melt-blends of polyethylene oxide and substantially water-insoluble compounds:

100 g of POLYOX® WSR N-80 is charged to a Cuisinart Pro Custom II™ mixing bowl. Distilled water is sprayed into the bowl as a fine mist at contents ranging from 5-15 phr (parts per hundred resin). The POLYOX® WSR and water are blended for approximately 2

-18-

minutes, after which the blender is stopped and any material stuck to the sides is scraped back into the mixing bowl. The material is then re-blended for another 2 minutes. At this point, the active is introduced (25 g) and the entire granulation is blended for an additional 2 minutes, collected and stored in polyethylene bags at 5 °C for further use. Free-flowing granulations were still evident after addition of the active.

50 g of the granulation was charged to a Brabender Plasticorder equipped with twin-screw mixing heads. The bowl temperature ranged from 80 °C-120 °C, depending upon which active was used. The test speed in all cases was 30 rpm. Upon addition of the granulation to the mixing bowl, the temperature dropped by 5 °C -10 °C, and after fusion slowly climbed back up to the set point. The material was allowed to mix for 2-3 minutes. The run was then stopped, and the fused material was spooned out of the mixing bowl and allowed to cool isothermally on metal platens until reaching room temperature. The final composition was somewhat tacky in nature.

The melt fused materials obtained from the Brabender were compressed into plaques on a Greenard Press. The plaques had dimensions of 63 mm x 63 mm x 3 mm. The heating cycle for each system regardless of active was as follows: 1 min heat with no pressure at 80 °C, 1 min heat with pressure at 2,000 psi, followed by isothermal cooling to room temperature. Teflon® Release paper was used to separate the material from the top plaque in all cases. From these plaques, tablets were punched out that weighed 3.5 g.

These tablets were placed in 100 mL volumetric flasks containing distilled water and placed on a magnetic stir plate at 25 °C. The concentration (%w/v) of the POLYOX WSR solutions explored

ranged from 0.5 to 2.0. An excess of drug was present in each solution forming a saturated solution which was allowed to stir for 2 hours at 23 °C.

At the end of this period, small aliquots were removed and filtered through 0.45m filters and the filtrates were suitably diluted and blanked for absorbance measurements at the appropriate wavelength using a UV-VIS spectrophotometer. Drug solubility was determined from established calibration curves. Table 5 illustrates the use of a low molecular weight polyethylene oxide resin with tolbutamide.

From Table 5, it can be seen that the maximum solubility of tolbutamide in water (pH=7.0) and simulated gastric fluid (pH=1.1) is approximately 70 ppmw. With simple addition of polyethylene oxide to the aqueous solution, a 3 fold or 300% increase in tolbutamide solubility is evident. A similar increase in SGF is evident, a little more than a 2 fold increase is apparent.

Quite surprisingly, upon inspection of the melt blends at 5, 10, and 15 phr an even larger increase in drug solubility is evident. For example, at 5 phr, tolbutamide solubility in water has increased over 10 fold relative to tolbutamide in water alone. This increase is much larger than what had been observed by simply mixing the polymer and drug alone in solution. Without being bound to any particular theory or concept, it appears that the increased solubilization of the drug prepared by the melt blending technique may be a result of better mixing and increased polymer-drug interactions in the melt phase, which leads to a greater interaction between polymer and drug, thus enhancing water solubility. Regardless of plasticizer concentration

used in this study, the increase in drug solubility in water in all cases was the same, that is a 10 fold increase.

A similar trend is also evident in the solubility profile of the melt blend in SGF. All blends appear to enhance the solubility of tolbutamide by 8 fold. The physical blends only increased solubility by a little over 2 fold. A distinct advantage of the current invention allows one to increase the solubility of substantially water-insoluble drugs in media with varying pH's by melt mixing with a hydrophilic thermoplastic polyethylene oxide. More importantly, low processing temperatures can be used to minimize drug degradation during manufacture.

Table 5

Solubility of tolbutamide in POLYOX WSR N-80 dispersions and melt blends in H<sub>2</sub>O and SGF.

Sample	POLYOX WSR Conc (%w/v)	Plasticizer Conc (phr) <sup>c</sup>	Medium	Solubility (ppm)
1	0.0	0.0	H <sub>2</sub> O	70
2	0.0	0.0	SGF	70
3 <sup>a</sup>	1.0	0.0	H <sub>2</sub> O	225
4 <sup>a</sup>	1.0	0.0	SGF	125
5 <sup>b</sup>	1.0	5.0	H <sub>2</sub> O	900
6 <sup>b</sup>	1.0	5.0	SGF	575
7 <sup>b</sup>	1.0	10.0	H <sub>2</sub> O	925
8 <sup>b</sup>	1.0	10.0	SGF	610
9 <sup>b</sup>	1.0	15.0	H <sub>2</sub> O	900
10 <sup>b</sup>	1.0	15.0	SGF	650

a: physical dispersion.

b: melt blend

c: parts per hundred resin (water is the plasticizer)

### EXAMPLE 6

To determine if polyethylene oxides have similar effects on other drugs, melt fused samples were prepared with sulfathiazole, following the procedure outlined in Example 5. The data for this system is illustrated in Table 6. From this table, when melt mixing this drug with polyethylene oxide, the solubility of sulfathiazole has increased over 2 fold. The same is not true for a physical dispersion, where the drug solubility stays unchanged. Once again, melt mixing the substantially water-insoluble compound and polymer imparts enhanced solubility not evident when both materials are dispersed in water. The increase in solubility is greater than 200%.

Table 6

Solubility of sulfathiazole in POLYOX WSR N-80 dispersions and melt blends in H<sub>2</sub>O.

Sample	POLYOX WSR conc (%w/v)	Plasticizer Conc (phr) <sup>c</sup>	Solubility (ppm)
1	0.0	0.0	550
2 <sup>a</sup>	1.0	0.0	605
3 <sup>b</sup>	1.0	5.0	1225

a: physical dispersion

b: melt blend

c: parts per hundred resin (water is the plasticizer)

### EXAMPLE 7

To further determine if polyethylene oxides have similar effects on other drugs, melt fused samples were prepared with hydroflumethazide, following the procedure outlined in Example 5. The data for this system is illustrated in Table 7. From this table,

-22-

when melt mixing this drug with polyethylene oxide, the solubility of hydroflumethazide has increased slightly over 2 fold. The same is not true for a physical dispersion, where the drug solubility stays relatively unchanged. Once again, melt mixing the substantially water-insoluble compound and polymer imparts enhanced solubility not evident when both materials are dispersed in water.

Table 7

Solubility of hydroflumethazide in POLYOX WSR N-80 dispersions and melt blends in H<sub>2</sub>O and SGF.

Sample	POLYOX WSR Conc (%w/v)	Plasticizer Conc (phr) <sup>c</sup>	Medium	Solubility (ppm)
1	0.0	0.0	H <sub>2</sub> O	400
2	0.0	0.0	SGF	275
3 <sup>a</sup>	0.5	0.0	H <sub>2</sub> O	500
4 <sup>a</sup>	0.5	0.0	SGF	480
5 <sup>b</sup>	0.5	5.0	H <sub>2</sub> O	1075
6 <sup>b</sup>	0.5	5.0	SGF	1025

a: physical dispersion

b: melt blend

c: parts per hundred resin (water is the plasticizer)

EXAMPLE 8

To determine the dissolution profile or rate of drug release over time from the physical and melt blends, a dissolution apparatus used was similar to the one employed by Mura and co-workers (P. Mura et al. *Il Farmaco.-Ed. Pr.* vol. 42 6, 149, 1987). The dissolution medium consisted of either 300 mL of distilled water or 0.1N HCl (SGF)



-23-

maintained at 23 °C in a 600 mL beaker covered with a glass plate. The amount of drug in each POLYOX WSR matrix tablet was greater than 1000 ppm. Two techniques were used to prepare tablets. The first technique produced tablets by directly compressing and had dimensions of 28 mm x 5 mm at a pressure of 2 tons and dwell time of 10 seconds on a Carver Press [Model C, Carver Lab Press, Menomonee Falls, WI].

In the second technique, tablets were prepared by using a whole punch on the compression molded plaques of POLYOX WSR. The geometry's and weights of both tablets varied less than 0.01 g.

The tablets were placed in a beaker and stirring was conducted at 200 rpm using a 5-blade paddle mixer. At suitable time intervals, 5 mL aliquots were removed from the dissolution vessel (600 mL beaker) and filtered with 0.45m filters and replaced with 5 mL of fresh dissolution medium. The amount of drug in solution at each time interval was appropriately diluted and blanked for absorbance measurements using a UV-VIS. Drug solubility was determined from established calibration curves as a function of time.

Table 8 lists the rate of drug dissolution over time for polyethylene oxide samples in water prepared by melt blending and physical dispersion. From this table, it can be observed that the amount of drug released over time is much greater for the melt blends compared to the physical blends. Also, the total solubility of the melt blend system is greater than the physical blend system. This release rate data correlates well with the increase in solubility discussed in Example 5.

Table 8.

In vitro solubility of tolbutamide in water from physical and melt blends at 23 °C

<u>Time (hr)</u>	<u>Physical Blend Solubility (ppm)</u>	<u>Melt Blend Solubility (ppm)</u>
0.0	0	0
0.3	160	220
1.0	255	480
2.0	380	660
3.0	410	870
4.0	360	840
5.0	400	830
6.0	330	720
7.0	350	700

EXAMPLE 9

Table 9 lists the rate of tolbutamide dissolution over time for polyethylene oxide samples in SGF prepared by melt blending and physical dispersion. From this table, it can be observed that the amount of drug released over time is much greater for the melt blends compared to the physical blends. Also, the total solubility of the melt blend system is much greater than the physical blend system. This release rate data correlates well with the increase in solubility discussed in Example 5.

-25-

Table 9.

In vitro solubility of tolbutamide in SGF from physical and melt blends  
at 23 °C

<u>Time</u> <u>(hr)</u>	<u>Physical Blend</u> <u>Solubility (ppm)</u>	<u>Melt Blend</u> <u>Solubility (ppm)</u>
0.0	0	0
0.3	51	65
1.0	90	230
2.0	109	420
3.0	100	525
4.0	105	562
5.0	110	510
6.0	103	565
7.0	105	520

EXAMPLE 10

Table 10 lists the rate of sulfathiazole dissolution over time for polyethylene oxide samples in water prepared by melt blending and physical dispersion. From this table, it can be observed that the amount of drug released over time is somewhat greater for the melt blends compared to the physical blends. Also, the total solubility of the melt blend system is greater than the physical blend system. This release rate data correlates well with the increase in solubility discussed in Example 6.

Table 10.

In vitro solubility of sulfathiazole in water from physical and melt blends at 23 °C

<u>Time (hr)</u>	<u>Physical Blend Solubility (ppm)</u>	<u>Melt Blend Solubility (ppm)</u>
0.0	0	0
0.3	480	620
1.0	600	720
2.0	540	880
3.0	660	704
4.0	480	820
5.0	460	920
6.0	580	720
7.0	560	560

EXAMPLE 11

Table 11 lists the rate of hydroflumethazide dissolution over time for polyethylene oxide samples in water prepared by melt blending and physical dispersion. From this table, it can be observed that the amount of drug released over time is much greater for the melt blends compared to the physical blends. Also, the total solubility of the melt blend system is greater than the physical blend system. This release rate data correlates well with the increase in solubility discussed in Example 7.

Table 11.  
In vitro solubility of hydroflumethazide in water from physical and  
melt blends at 23 °C

<u>Time</u> <u>(hr)</u>	<u>Physical Blend</u> <u>Solubility (ppm)</u>	<u>Melt Blend</u> <u>Solubility (ppm)</u>
0.0	0	0
0.3	110	500
1.0	300	1100
2.0	375	1280
3.0	220	704
4.0	230	540
5.0	260	500
6.0	230	410
7.0	265	440

EXAMPLE 12

Table 12 lists the rate of hydroflumethazide dissolution over time for polyethylene oxide samples in SGF prepared by melt blending and physical dispersion. From this table, it can be observed that the amount of drug released over time is much greater for the melt blends compared to the physical blends. Also, the total solubility of the melt blend system is much greater, 4 to 5 times than the physical blend system. This release rate data correlates well with the increase in solubility discussed in Example 7.

Table 12.  
In vitro solubility of hydroflumethazide in SGF from physical and melt  
blends at 23 °C

<u>Time</u> <u>(hr)</u>	<u>Physical Blend</u> <u>Solubility (ppm)</u>	<u>Melt Blend</u> <u>Solubility (ppm)</u>
0.0	0	0
0.3	215	420
1.0	350	1040
2.0	320	1400
3.0	215	1600
4.0	230	1400
5.0	400	2100
6.0	390	1560
7.0	375	1560

A critical parameter to the methods described above for enhancing the water solubility of substantially water-insoluble compounds with carriers like polyethylene oxides is the shelf-life stability of such compounds. Certain carriers, for example polyvinyl pyrrolidone and polyethylene glycols, when formulated with the substantially water-insoluble compounds, alter the structure of the substantially water-insoluble compound from the crystalline to the amorphous state. The problem with such a morphological change is that the drug, over time, may re-crystallize, thus reducing its water-solubility. Such trends have been seen in PEG 6000-tolbutamide systems (Kedzierewicz et al. *Int. J. Pharm.* 117, 247, 1995). Their findings show that upon storage, the dissolution profiles for melt

-29-

mixtures of PEG 6000 and tolbutamide change over time. The explanation for this change in dissolution profile probably corresponds to an increase in crystallinity of tolbutamide over a 6 month storage period at 37 °C. Other examples include the use of PEG 6000 with indomethacin, where crystallization of the drug reduced the dissolution rate of the active (Saboe et al. *Drug. Dev. Comme.* 2, 359, 1976). Other examples where changes in dissolution profiles have been documented have included the use of nifedipine-polyvinyl pyrrolidone (PVP) based systems (Sugimoto et al. *Drug. Dev. Ind. Pharm.* 6, 137, 1980), indomethacin-PEG 6000 (Ford et al. *Pharma. Acta Helv.* 54, 353, 1979), and diazepam-PEG 4000 (Anastasiadou et al. *Drug. Dev. Ind. Pharm.* 9, 103, 1983). In these systems, it was found that humidity was a major cause for increasing crystallinity of the substantially water-insoluble compound.

There is a growing need for stable, long-lasting formulations that do not change over time. The following example addresses this concern.

### EXAMPLE 13

The preparation from Example 5 was stored at room temperature for almost one year and re-tested in both SGF and distilled water. Table 13 lists the UV-max for this system at t=0 days in water and t=355 days. Notice, the absorption at 228 nm is 1.51 AU. Quite surprisingly, when this sample was re-run, the absorption at 228 nm was 1.52 AU. The solubility of the drug in water did not change over time.

The same was true for the solubility of this sample in SGF as can be seen in Table 14. The maximum absorbance for the sample

-30-

at  $t=0$  was 1.64 AU. Quite surprisingly, at  $t=335$  days, the maximum absorbance at 228 nm is still 1.65 AU. The solubility of the drug in SGF has not changed over time.

Table 13.

Solubility of tolbutamide in water from melt blend of POLYOX WSR N-80 stored at 23 °C for 335 days.

Sample	Time (days)	Solubility (ppm)	Wavelength Result (AU)
1	0	900	1.51
2	335	900	1.52

Table 14.

Solubility of tolbutamide in SGF from melt blend of POLYOX WSR N-80 stored at 23 °C for 335 days.

Sample	Time (days)	Solubility (ppm)	Wavelength Result (AU)
1	0	590	1.64
2	335	610	1.65

This example clearly illustrates the usefulness of polyalkylene oxides in enhancing the water solubility of a substantially water-insoluble compounds and that this increase in solubility does not change over time.



#### EXAMPLE 14

In this example, tolbutamide, was formulated with both POLYOX WSR and a low molecular weight polyethylene glycol. The POLYOX WSR sample was prepared as described in Example 5. The polyethylene glycol sample was prepared as described in Example 1. The results are summarized in Table 15. From this table it can be seen that, at a relatively high polymer concentration of 5.0% (w/v), the polyethylene glycol did not substantially increase the solubility of tolbutamide (less than 10.0%). Quite surprisingly, this is not true for the high molecular weight polyethylene oxide. The solubility enhancement of this system is over 800% at a polymer concentration of only 1.0% (w/v).

High molecular weight polyethylene oxides not only increase the solubility of substantially water-insoluble compounds like tolbutamide at low pH's, but also the amount of polymer needed for this enhancement is five times lower than what is needed for polyethylene glycols. Further, by using a high molecular weight polyethylene oxide, one can impart a controlled delivery of the substantially water-insoluble compound over a long period of time. Low molecular weight polyethylene glycols dissolve rapidly and can not afford such a delivery profile.

Table 15.  
Solubility of tolbutamide in SGF prepared from POLYOX WSR N-80  
and CARBOWAX PEG 8,000.

Sample	Polymer	Conc. (% w/v)	Solubility (ppm)
1	none	0.0	70
2	PEG 8,000	5.0	80
3	WSR N-80	1.0	575

Although the present invention has been described with respect to specific aspects, those skilled in the art will recognize that other aspects are intended to be within the scope of the claims which follow.

We Claim

1. A method for enhancing the water-solubility of a substantially water-insoluble compound having a water-solubility of less than about 1000 ppmw, comprising combining said compound with a water-soluble polymer having a weight average molecular weight of from about 50,000 to 7,000,000 grams per gram mole and a water-solubility of at least about 1.0 weight percent in an amount effective to increase the water-solubility of said compound in an acidic environment by at least about 10 percent.
2. The method of claim 1 wherein the water-soluble polymer has alkylene oxide functionality.
3. The method claim 2 wherein the water-soluble polymer is a polyalkylene oxide.
4. The method of claim 2 wherein the water-soluble polymer is an alkoxylated polysaccharide.
5. The method of claim 4 wherein the water-soluble polymer is a cellulose ether.
6. The method claim 1 comprising physically blending said substantially water-insoluble compound and said water-soluble polymer.

-34-

7. The method of claim 6 comprising melting said water-soluble polymer prior to, or during, said blending.

8. A composition comprising a substantially water-insoluble compound having a water-solubility of less than about 1000 ppmw and a water-soluble polymer having a weight average molecular weight of from about 50,000 to 7,000,000 grams per gram mole and a water-solubility of at least about 1.0 weight percent in an amount effective to increase the water-solubility of said compound in an acidic environment by at least about 10 percent.

9. The composition of claim 8 in the form of a solid.

10. The composition of claim 8 in the form of a solid.



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# INTERNATIONAL SEARCH REPORT

International Application No

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**A. CLASSIFICATION OF SUBJECT MATTER**  
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**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 012 523 A (AMERICAN HOME PRODUCTS) 25 June 1980 see page 2, line 1 - line 17 see page 16 - page 20; example 6 ---	1,2,4-6, 8-10
X	EP 0 315 964 A (FUJISAWA PHARMACEUTICAL CO. LTD.) 17 May 1989 see page 2, line 18 - line 29 see page 9, line 9 - page 11, line 39 ---	1,2,4-6, 8-10
X	WO 96 32097 A (PHARMA PASS) 17 October 1996 see claims 1,6,19 ---	8-10
E	WO 98 11879 A (DEPOMED, INC.) 26 March 1998 see claims 1,4 -----	8-10

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 12523 A	25-06-1980	AT 5852 T US 4344934 A	15-02-1984 17-08-1982
EP 315964 A	17-05-1989	CA 1319110 A DE 3877331 A ES 2043766 T JP 2000206 A PH 26518 A US 5093372 A	15-06-1993 18-02-1993 01-01-1994 05-01-1990 07-08-1992 03-03-1992
WO 9632097 A	17-10-1996	AU 5652796 A EP 0830129 A	30-10-1996 25-03-1998
WO 9811879 A	26-03-1998	AU 4428097 A	14-04-1998